PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 19.10.21 PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2005/002157	International filing date *(day/month/year)* 24.02.2005	Priority date *(day/month/year)* 24.02.2004

International Patent Classification (IPC) or national classification and IPC
INV. A61M11/00

Applicant
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1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 10 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand 22.12.2005	Date of completion of this report 12.05.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Kroeders, M Telephone No. +31 70 340-1967

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/002157

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3(a) and 23.1(b))
   ☐ publication of the international application (under Rule 12.4(a))
   ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

2-9, 12-42	as originally filed
1, 1a, 10, 11, 11a	filed with the demand

Claims, Numbers

1-34	filed with the demand

Drawings, Sheets

1/6-6/6	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/002157

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-34
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-34
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-34
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V.

1 Reference is made to the following documents:
D1 : US 4 674 490 A (FRANKEL ET AL) 23 June 1987 (1987-06-23)
D2 : US 5 800 598 A (CHEIN ET AL) 1 September 1998 (1998-09-01)
D3 : US 6 105 877 A (COFFEE ET AL) 22 August 2000 (2000-08-22)

2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

2.1 Document D1 discloses (the references in parentheses applying to this document):

> an inhalation device for creating an aerosol, comprising:
> aerosol means (24), for creating an aerosol,
> control means, for manipulating state and condition of the aerosol, in order to thereby control the particle size of the aerosol (see column 5, lines 45 to 49 and column 2, lines 3 to 19), wherein
> the device is provided with supply means (54) for adding a substance to the aerosol, prior to or upon release of the aerosol from the device

The device of claim 1 differs from this disclosure in that the control means controls the particle size of the aerosol itself by adding or removing energy from the aerosol, prior to the adding of the substance. The aerosol carrying the substance is then released from the device through an opening.

This feature solves the problem of providing accurate control over the particle size of the aerosol.

This feature involves an inventive step according to Article 33(3) PCT, as it allows the device to modify the particle size of the (carrier) aerosol after its generation, before the addition of the additional substance.

None of the prior art documents as currently available (D1, D2 or D3) disclose the same feature for the same purpose.

3 The device disclosed in claim 1 is industrial applicable and therefore the requirements of Article 33(4) PCT are met as well.

4 Claims 2 to 23 depend from claim 1 and refer to further embodiments of the device described in claim 1 and thus meet the requirements of Articles 33(2), (3) and (4) PCT for the same reasons explained above.

5 Claims 24 to 34 were originally not searched, but correspond to the method of the use of the device according to claim 1. These claims meet the requirements of Articles 33(2), (3) and (4) PCT for the same reasons explained above.

Inhalation device for creating an aerosol

Field of the invention

The present invention relates to an inhalation device for creating an aerosol, wherein the device comprises:

- aerosol means, for creating an aerosol in the device,
- control means, for manipulating the aerosol by adding energy to or removing energy from the aerosol to adjust the state and condition of the aerosol, in order to control the characteristics of the aerosol, such as uniformity and mean particle size, and
- an opening, for releasing the aerosol from the device.

The present invention is specifically suitable for pulmonary delivery of substances, such as drugs.

Background of the invention

Traditional drug delivery methods – except injection and infusion – are used primarily with small molecules, such as individual peptides. Pulmonary delivery is already in use for a variety of small-molecule drugs, mainly to treat respiratory disorders. Drugs with respiratory applications include anti-inflammatory agents, bronchodilators and protease inhibitors. Yet, the deep lung is also a favourable environment for non-invasive delivery and absorption of large molecules – as the alveoli (deep lung) provide an extensive air-blood interface allowing large-molecule proteins and peptides access to the body's systemic circulation. Therefore pulmonary drug delivery has the potential to be a much more effective route of administration of macromolecules, with a relatively higher bioavailability than with any other route except injection or infusion. In addition the development of deep lung delivery devices may increase patient acceptance and improve compliance – as an alternative to the invasiveness of injection.

Pulmonary delivery applies to substances with different aggregate conditions: gas, liquid or solid, which may be inhaled both through the nose and the mouth, with the intention to have either a medical or a non-medical effect. Substances for inhalation may be targeted at the

body's systemic circulation system, but likewise they may be aimed to have a topical effect from the point of administration onwards, i.e. from the mouth/nose through to the deep lung.

With reference to the above an object of the present invention is to improve the administration of a substance to a mammal by means of inhalation.

According to a first aspect of the invention this object is achieved in that the invention provides an inhalation device for creating an aerosol, comprising:

- aerosol means, for creating an aerosol in the device,
- control means, for manipulating the aerosol by adding energy to or removing energy from the aerosol to adjust the state and condition of the aerosol, in order to control the characteristics of the aerosol, such as uniformity and mean particle size, and
- an opening, for releasing the aerosol from the device,

wherein:

- the device is provided with supply means, for adding a substance to the aerosol, prior to or upon release of the aerosol from the opening, in order to release the substance from the opening using the aerosol as a carrier.

The device according to the invention may comprise process means, coupled with the control means, provided with storage means, for receiving and processing data relating to a preferred state and condition of the aerosol prior to adding a substance to the aerosol and prior to being released.

According to a second aspect of the invention a method is provided for creating an aerosol in an inhalation device, comprising the steps of:

a) creating an aerosol by means of aerosol means in the inhalation device,
b) manipulating the aerosol by adding energy to or removing energy from the aerosol to adjust the state and condition of the aerosol, in order to control the characteristics of the aerosol, such as uniformity and mean particle size, and
c) releasing the aerosol from an opening of the device,

wherein the method comprises the step of:

d) adding a substance to the aerosol, prior to or upon release of the aerosol from the device, in order to release the substance from the opening using the aerosol as a carrier.

According to the invention step d) is executed after the completion of step b) and prior to or upon step c). Step b) may be repeated after the completion of step d).

It is possible that the method comprises the step of:

e) prior to step b) identifying a preferred state and condition of the aerosol to be released from the device.

According to the invention steps e) is executed prior to step b). Step e) may be repeated after the completion of step d).

A result of these measures is the ability to control the conditions of a mixture of an aerosol carrier and a substance added to this aerosol before inhalation, in order to positively influence the deposition behaviour of the substance to be inhaled and the intended effect of the substance.

The aerosol is used as a carrier means for transporting a substance, such as a drug, to the respiratory tract and lungs of a mammal. In a first phase the aerosol is manipulated in order to present optimal characteristics to transport a substance to be administered to the mammal. The aerosol may be manipulated in order to also comply with comfort requirements of the mammal. That means that upon release from the device the loaded aerosol may have a preferred temperature, carrier particle concentration, particle size, uniformity and relative humidity.

In a second phase the substance is added to the aerosol carrier. This has as an advantage that the aerosol can be manipulated without the need of taking care of the stability, integrity or other conditions of the substance. As a further advantage, the substance can be stored in a high concentration without the need of adding a carrier material. The substance does not have to contain a carrier in order to be administered. The substance can in any preferred aggregation be added to the aerosol carrier and be transported to the mammal therewith.

Further preferred embodiments and characteristics of the invention are described in the depending claims.

Further objects, advantages and features of the invention will become apparent upon reading the detailed description of the invention in combination with the drawings.

Brief description of the drawings

Fig. 1 shows schematically the production of a vapour by means of a fuel cell;

Claims

1. Inhalation device for creating an aerosol, comprising:

- aerosol means, for creating an aerosol in the device,
- control means, for manipulating the aerosol by adding energy to or removing energy from the aerosol to adjust the state and condition of the aerosol, in order to control the characteristics of the aerosol, such as uniformity and mean particle size, and
- an opening, for releasing the aerosol from the device,

wherein:

- the device is provided with supply means, for adding a substance to the aerosol, prior to or upon release of the aerosol from the opening, in order to release the substance from the opening using the aerosol as a carrier.

2. Device according to claim 1, wherein the aerosol means comprises a mist generator.

3. Device according to claim 1, wherein the aerosol means comprises a catalytic burner, such as a fuel cell.

4. Device according to one of the preceding claims, wherein the device comprises an aerosol chamber for creating the aerosol in said chamber.

5. Device according to one of the preceding claims, wherein the control means comprises a condensation chamber.

6. Device according to claim 5 wherein the condensation chamber has a first open end to receive a flow and a second open end to release a flow.

7. Device according to claims 5 or 6, wherein the condensation chamber adjoins the aerosol chamber.

8. Device according to one of the preceding claims, wherein the control means comprises a heat exchanger provided with apertures for allowing the aerosol to pass through the heat exchanger.

9. Device according to one of the claims 5 - 8, wherein the device comprises a Peltier-element, positioned in the condensation chamber, to retrieve condensation energy.

10. Device according to one of the preceding claims, wherein the control means comprises dilution means for mixing the aerosol with a fluid, such as an unsaturated gas, for thereby decreasing the dew point of the aerosol.

11. Device according to one of the preceding claims, wherein the supply means comprises means for adding a gaseous substance to the aerosol.

12. Device according to claim 11, wherein the supply means comprises a container, such as a canister, for storing a gaseous substance.

13. Device according to one of the preceding claims, wherein the supply means comprises means for adding a liquid substance to the aerosol.

14. Device according to claim 13, wherein the supply means comprises a membrane pump.

15. Device according to one of the preceding claims, wherein the supply means comprises means for adding a solid substance to the aerosol.

16. Device according to claim 13 or 15, wherein the supply means comprises a container for storing a propellant, such as CO_2 , and a liquid and/or solid substance.

17. Device according to one of the preceding claims, wherein the device is adapted to be breath actuated.

18. Device according to one of the preceding claims, wherein the device is provided with means for operating the device with a breath support.

19. Device according to one of the preceding claims, wherein the control means are coupled with process means, provided with storage means, for receiving and processing data relating to a preferred state and condition of the aerosol to be released.

20. Device according to claim 19 wherein the device is provided with sensor means, coupled with the process means, to measure data relating to the state and condition of the aerosol to be released.

21. Device according to one of the preceding claims, wherein the supply means are coupled with process means, provided with storage means, for receiving and processing data relating to a preferred timing of the adding of the substance to the aerosol.

22. Device according to claim 21 wherein the device is provided with sensor means, coupled with the process means, to measure data relating to the timing of the adding of the substance to the aerosol.

23. Device according to claim 20 or 22, wherein the sensor means comprise flow measurement means for producing a measure of volume released.

24. Method for creating an aerosol in an inhalation device, comprising the steps of:

a) creating an aerosol by means of aerosol means in the inhalation device,

b) manipulating the aerosol by adding energy to or removing energy from the aerosol to adjust the state and condition of the aerosol, in order to control the characteristics of the aerosol, such as uniformity and mean particle size, and

c) releasing the aerosol from an opening of the device,

wherein the method comprises the step of:

d) adding a substance to the aerosol, prior to or upon release of the aerosol from the device, in order to release the substance from the opening using the aerosol as a carrier.

25. Method according to claim 24, wherein the method comprises the step of:

e) prior to step b) identifying a preferred state and condition of the aerosol to be released from the device.

26. Method according to claim 24 or 25, wherein step d) is executed after the completion of step b).

27. Method according to one of the claims 24 – 26, wherein step b) is repeated after the completion of step d).

AMENDED SHEET

28. Method according to claim 24 – 27, wherein the method comprises the step of:

f) measuring the actual flow through the device, and

g) using this measurement in order to control the manipulation of the aerosol in step b).

29. Method according to one of the claims 24 – 28, wherein the method comprises the step of:

h) prior to step b) evaluating the heat content of the aerosol in order to thereby determine the specific amount of energy to be added or extracted from the aerosol in order to realise the desired manipulation of the aerosol.

30. Method according to one of the claims 24 – 29, wherein the manipulation of the aerosol comprises a condensation step, for allowing condensation of at least part of the gaseous phase of the aerosol.

31. Method according to claim 30, wherein the manipulation of the aerosol is adapted to obtain an aerosol with a relative humidity of 100%.

32. Method according to one of the claims 24 – 31, wherein the manipulation of the aerosol comprises a dilution step, for mixing the aerosol with a fluid, such as an unsaturated gas, for thereby decreasing the dew point of the aerosol.

33. Method according to one of the claims 25 – 32, wherein the method comprises the step of:

i) using the results of steps e) and f) to calculate a preferred timing for the adding of the substance to the aerosol.

34. Method according to one of the claims 24 – 33, wherein the method comprises the step of creating in step a) an aerosol containing a first substance and adding in step d) a further substance to said aerosol.

Abstract

The present invention relates to an inhalation device and a method for creating an aerosol in an inhalation device. The inhalation device according to the invention comprises:

- aerosol means, for creating an aerosol in the device,
- control means, for manipulating the aerosol by adding energy to or removing energy from the aerosol to adjust the state and condition of the aerosol, in order to control the characteristics of the aerosol, such as uniformity and mean particle size, and
- an opening, for releasing the aerosol from the device,

wherein:

- the device is provided with supply means, for adding a substance to the aerosol, prior to or upon release of the aerosol from the opening, in order to release the substance from the opening using the aerosol as a carrier.

The device according to the present invention is suitable for pulmonary delivery of substances, such as drugs.